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Original Article

Assessment of postoperative perfusion with contrast-enhanced ultrasonography in kidney transplantation

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Abstract: The aim of this study was to use contrast-enhanced ultrasound (CEUS) to evaluate renal perfusion after kidney transplantation and investigate the clinical significance of CEUS in monitoring postoperative renal perfusion. Thirty-five patients who underwent kidney transplantations were included in this study and divided into two groups-normal and abnormal-based on their serum creatinine (SCr) levels. Conventional ultrasound and CEUS were used to monitor renal perfusion after kidney transplantation. The differences in the results between the two groups were then compared. Color doppler ultrasonography showed that there were significant differences in the resistance index (RI) and the pulsatility index (PI) of the interlobar artery between the groups. Furthermore, CEUS indicated a significant difference between the two groups regarding the slope rate of the cortical ascending curve (A1), the medullary ascending curve (A2), and the derived peak intensity (DPI1). CEUS precisely showed the characteristics of microcirculation in renal parenchyma after kidney transplantation. It also detected changes in the microcirculation, which was a new method of evaluating tissue perfusion in transplanted kidneys.

Keywords: Transplant kidney, ultrasonic examine, color doppler ultrasound, contrast-enhanced ultrasound

Introduction

Nowadays, kidney transplantation is recognized as the best way to treat end-stage renal disease; thus, it has obtained more attention from hospitals, families, and societies. With the development of kidney transplantation techniques and the popularity of new immunosuppressive agents, the survival rates in patients with grafted kidneys have improved significantly [1]. However, the complications after renal transplantation are still important reasons for graft dysfunction and functional loss; therefore, if they can be detected and treated early, the postoperative survival rate can be greatly improved [2, 3].

The color doppler ultrasound can provide a lot of information about the transplanted kidney's morphology and blood circulation, simultaneously; thus, it was an important method to detect complications after renal transplantation. However, the color doppler ultrasound had limitations such as insensitivity to low blood flow and detection-angle dependence, which made it difficult to provide information about the renal microcirculation. Its role in assessing the perfusion in a transplanted kidney was thereby limited [4, 5].

The CEUS technology uses acoustic contrast, with the diameter of a microvesicle of only 3-8 μm, to enhance the ultrasonic images of tissues and organs based on the perfused microvascular bed, so that the tissue-blood fusion in solid organs can be understood. It can evaluate the physiological and pathological changes of solid organs through the quantitative analysis of blood flow [6, 7]. In recent years, the role of this technology in detecting complications post-renal transplantation has obtained increasing attention [8-10].

This study used the CEUS technology to evaluate the status of renal blood perfusion after renal transplantation and made comparisons

Table 1. Comparisons of 2-dimensional ultrasound and color Doppler ultrasound between normal group and abnormal group

Index	SCr Normal group	SCr Abnormal group
2-dimensional ultrasound		
Renal volume (cm^3)	172.42±37.22	208.24±114.53
Color Doppler ultrasound		
Segmental artery PSV	66.41±27.71	59.27±24.48
EDV	18.29±4.75	13.10±8.39
RI	0.70±0.19	0.74±0.10
PI	1.45±0.36	1.68±0.58
Interlobar artery PSV	54.20±17.23	48.09±12.77
EDV	15.23±4.50	11.09±5.73
RI	0.70±0.66	0.80±0.13*
PI	1.46±0.26	2.00±0.67*
Arcuate artery PSV	41.50±11.83	42.09±18.55
EDV	11.15±3.83	14.20±4.50
RI	0.74±0.26	0.77±0.34
PI	1.68±0.30	1.80±0.84

SCr normal group vs. SCr abnormal group *$P < 0.05$. PSV, peak systolic velocity; EDV, end diastolic velocity; RI, Resistance Index; PI, pulsatility index.

using the conventional color doppler ultrasound. The aims were to investigate its application values in monitoring the postoperative status of renal blood perfusion and to diagnose the complications; thus, provide new research methods for the early diagnosis and identification of renal transplantation complications.

Materials and methods

Study subjects

Thirty-five renal allograft recipients, who underwent kidney transplantation surgeries within 1-6 months in Beijing Chaoyang Hospital from January 2010 to December 2010, were included. Allograft recipients excluded from this study were patients who failed to survive, or underwent repeated transplantation operations, suffered from urinary obstruction, peri-renal hematoma, and local infection in the operative area. The participants included 28 males and 7 females, whose mean age was 37.3 years old (15-59 years). The 35 recipients were divided into two groups: a normal group, with serum creatinine (SCr) levels ≤ 140 μmol/L (24 cases) and an abnormal group with SCr > 140 μmol/L (11 cases) [11]. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Capital Medical University. Written informed consent was obtained from all participants.

Conventional ultrasound scan

Conventional two-dimensional ultrasound scan was performed by IU22 ultrasonoscope (PHILIP Company, Eindhoven, Holland) to observe kidney size and calculate kidney volume (length × width × thickness × π/6). Color Doppler flow imaging showed the blood supply of the transplanted kidney. Meanwhile, the peak systolic velocity (PSV), end diastolic velocity (EDV), and resistance Index (RI) of the segmental artery, interlobar artery, and arcuate artery were measured. Furthermore, the pulsatility index (PI) was also measured three times and the average value obtained.

Contrast-enhanced ultrasound

Contrast agent SonoVue (Bracco Company, Milan, Italy) was purchased from Bracco Company. Physiological saline (5 mL, 0.9% NaCl) was added to SonoVue solution, which was then shaken until CEUS was formed. IU22 ultrasonoscope showed the optimal sections of the vascular dendritic structure of the inner segment arteries, interlobar arteries, and arcuate arteries. A "bolus-like" injection was conducted to administrate 1 mL of contrast agent into the left forearm veins, followed by the injection of 5 mL of physiological saline. The imaging process was then recorded for 2 minutes. QLAB contrast ultrasound quantitative analysis software was used to observe contrastographic images. For quantitative analysis of renal tissue perfusion, the region of interest (ROI) was focused on the cortex and medulla respectively, but not the interlobar arteries and the arcuate arteries of the cortex. The ROI in the medulla was a square region with an inside diameter of 5 mm. The time-intensity curve was pictured by software. The parameters included the slope rate of the ascending curve (A), the time to peak (TTP), the derived peak intensity (DPI) and the area under the curve (AUC). *A* means the average speed of perfusion after the contrast agent was used. This is reflected in the perfusion rate

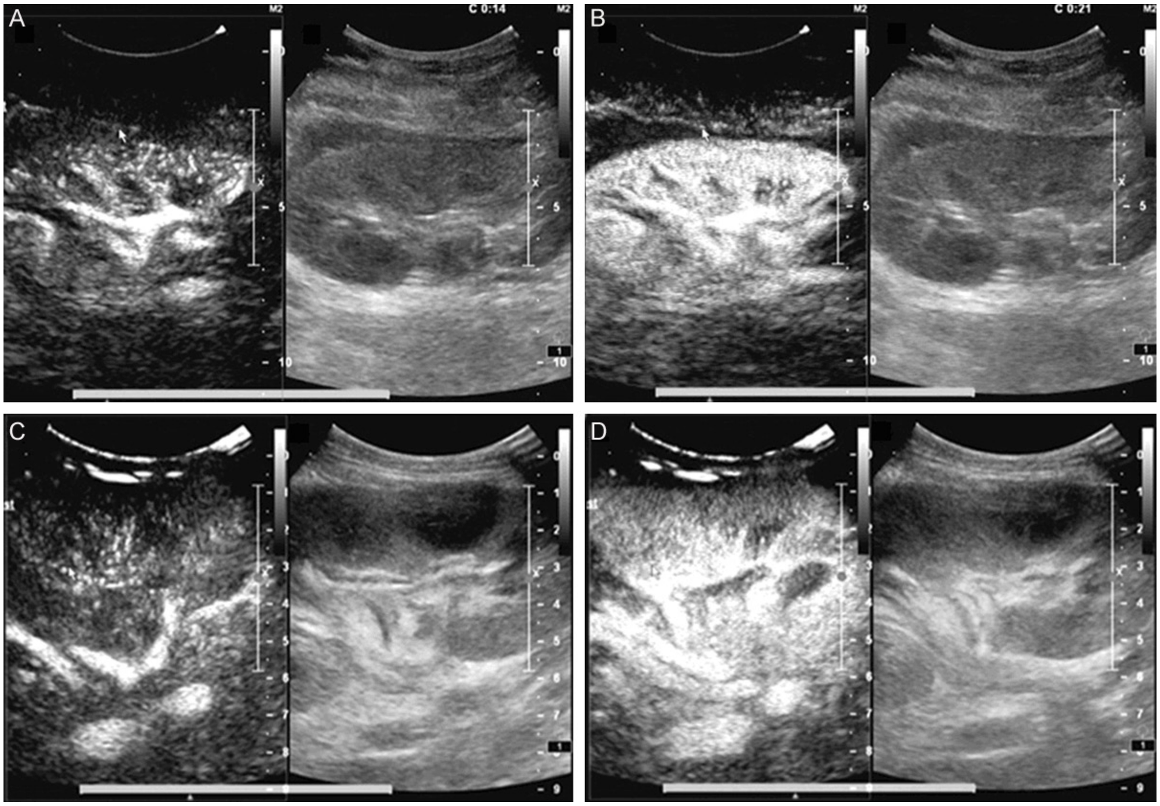

Figure 1. Images of contrast-enhanced ultrasound in SCr normal group and abnormal group. A: SCr normal patient: contrast agent reaching interlobar artery after 14 seconds. B: Contrast agent reaching corticomedullar after 21 seconds. C: SCr abnormal patient: contrast agent reaching interlobar artery after 43 seconds. D: Contrast agent reaching corticomedullar after 51 seconds.

of the local tissue. *TTP* means the time, which ranges from zero to a maximum, that the contrast agent reached the maximal intensity. *DPI* means that the contrast agent attained the peak intensity.

Statistical analysis

All data were presented as mean ± SD or mentioned as median and range. Independent samples group *t* test was used to compare the two groups. Differences were considered significant at $P < 0.05$. Statistical analysis was performed using SPSS17.0 software.

Results

Two-dimensional ultrasound and color doppler ultrasound scans

There was no significant difference between the two groups, in terms of the indices, with two-dimensional ultrasound. Color Doppler ultrasound showed that there were significant differences between the two groups regarding the RI of the interlobar artery ($t = 2.73$, $P = 0.03$) and PI ($t = 2.53$, $P = 0.02$). Other parameters showed no statistical significance (**Table 1**).

Contrast-enhanced ultrasound examination

Ultrasonogram of transplanted kidneys showed that the ultrasounds of the iliac arteries, renal arteries, segment arteries, interlobar arteries, arcuate arteries, and interlobular arteries were gradually enhanced after injection of the contrast agent, followed by enhancement of the renal cortex and medulla. However, the renal medulla started to enhance slower than the renal cortex. The contrast agent was perfused from the edge of each cone and then slowly enhanced to the center. The entire medulla was enhanced in order to spend more time on it than on the cortex. Generally, the cone center of the medulla was not enhanced when the contrast agent started to become weak. However, the transplanted kidney showed

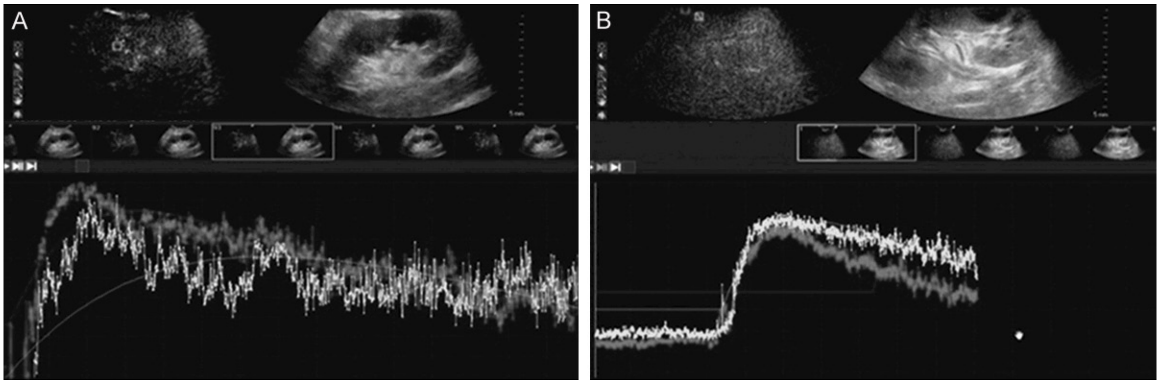

Figure 2. Time-intensity curve in SCr normal group and abnormal group. A: Normal group; B: Abnormal group. Red curve: time-intensity curve in cortex region. Yellow curve: time-intensity curve in medulla region.

Table 2. Comparisons of all parameters with CEUS between normal group and abnormal group ($\bar{x} \pm s$)

Group	A1	DPI1	TTP1	A2
SCr Normal	1.79±0.59	9.75±1.65	15.72±5.67	1.24±0.50
SCr Abnormal	1.27±0.57	7.45±3.38	19.00±8.05	0.87±0.42
t value	2.18	2.72	1.05	2.12
P value	0.03	0.01	0.29	0.04

A1: the slope rate of cortical ascending curve; A2: the slope rate of medullary ascending curve; DPI1: cortical derived peak intensity; TTP1: cortical time to peak.

uniform enhancement during nephrography (**Figure 1A**, **1B**). Meanwhile, this study showed that because of the SCr levels of the abnormal group, a longer time was necessary to make the cortex and medulla enhance completely when compared to the normal group. However, this result might be because of a subjective factor error (**Figure 1C**, **1D**).

Comparisons of TIC curve

There were significant differences between the normal group and the abnormal group in terms of the A1, A2, and DPI1 (**Figure 2**, $P < 0.05$). TTP1 was delayed in the SCr abnormal group, but it was not statistically significant ($P > 0.05$, **Table 2**; **Figure 3**).

Discussion

Although renal allograft is one of the most effective methods regarding therapy for end-stage renal failure, postoperative complication-especially rejection reaction-is a crucial cause of renal dysfunction. At present, complication is monitored by two-dimensional ultrasound, color Doppler ultrasound or renal resistance index [12].

Two-dimensional ultrasound scans the transplanted kidney and measures the kidney size, cortical and medullary thickness, and observes the entire kidney histology [13]. Previous study indicated that volume, cortex and medulla change in the transplanted kidney at the time of rejection [14]. Two-dimensional ultrasound reflected general renal structure and not flow condition in the kidney. Our results showed that the above indices of renal function in transplanted kidneys were not significantly different, thereby indicating that changes in size, thickness of the cortex and medulla, and kidney volumes were non-specific.

Color Doppler ultrasound distinctly showed the hemodynamic conditions of the renal arterial branch vessels. However, since the flow signal of the renal artery is affected by flow speed and detection angle, one ultrasound cannot indicate the exact perfusion condition. Moreover, color Doppler ultrasound is not sensitive to slow blood flow and is dependent on the detection angle to show poor micro-perfusion in a transplanted kidney. Our results show no significant difference between the normal group and the abnormal group in terms of the peak systolic velocity (PSV) and the end diastolic velocity (EDV) of the segmental artery, interlobar artery, and arcuate artery.

The resistance index (RI) is an important index to assess renal allograft dysfunction. Radmehr et al. [15] reported that Doppler examinations were done in all patients three times during the first week on days one, three, and five post-

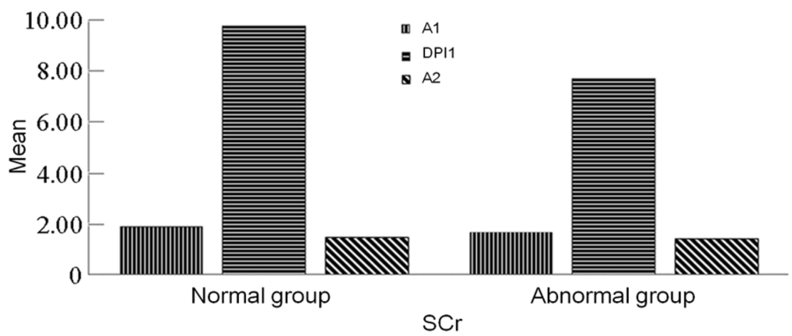

Figure 3. Comparisons of all parameters in SCr normal group and SCr abnormal group with CEUS technique.

transplantation and suggested that the mean RI and PI were both noticeably increased in patients with complications. Tarzamni et al. [16] and Nezami et al. [17] found that the SCr levels were high in renal allograft recipients and that RI and PI were also significantly correlated with the SCr levels. There was a linear correlation between the RI, PI, and Cr (r = 0.126). Thus, the RI, PI, and SCr level were markers to predict renal allograft function.

However, there was obvious uncertainty for RI. For example, blood intima-media thickness, intervention of pulse pressure, and impulse speed affect the RI value. Whether 0.8 was the best threshold value to reflect the transplanted kidney condition is still not certain. Only an increase in RI was not sufficient to assess renal function, acute renal tubular necrosis, calcineurin inhibitor toxicity, and rejection [13, 18, 19]. Based on the above reasons, an increased RI value was limited to chronic rejection reaction. This study suggests that the RI and PI of the segmental and arcuate arteries indicate no significant difference between the SCr normal group and the SCr abnormal group, but there was a significant difference between the two groups regarding the RI and PI of the interlobar artery, thereby indicating that the RI was uncertain in predicting transplant kidney lesion.

Tissue perfusion and pathological changes of solid organ through quantitative analysis to blood flow are understood by contrast-enhanced ultrasound (CEUS) technology, which uses acoustic contrast to enhance tissue and organ image. SonoVue is a new contrast agent and the micro-bubble diameter was only 3-8 μm. Furthermore, SonoVue is metabolized through the pulmonary circulation. Additionally, SonoVue only exists in the vessel and does not enter the tissue space; moreover, SonoVue could stay in the vessel for an adequate time in order to meet clinical needs. Because the micro-bubble exists in the vessel and reaches to micro-vessels of all tissues easily, contrast imaging provides blood perfusion information of all organs involved in the microcirculation.

Ultrasonogram of the transplanted kidney showed that the ultrasounds of the iliac arteries, renal arteries, segment arteries, interlobar arteries, arcuate arteries, and interlobular arteries were gradually enhanced, followed by enhancement of the renal cortex and medulla. However, the renal medulla started to enhance at a slower rate than the renal cortex. The contrast agent was perfused from the edge of each cone and then slowly enhanced to the center. The entire medulla was enhanced in order to spend more time on it than on the cortex. Generally, the cone center of the medulla was not enhanced when the contrast agent started to become weak. However, the transplanted kidney was uniformly enhanced during the process of nephrography. Meanwhile, this study showed that more time was necessary for completely enhancing the cortex and medulla in the SCr normal group compared to the SCr abnormal group. However, this result might be because of a subjective factor error.

With the application of real-time in contrast ultrasound, exact quantitative analysis has been made possible in recent years. According to the change of the echo signal intensity of the contrast agent in the region of interest (ROI), the contrast agent time-intensity curve was established to get relative quantitative parameters, such as time to peak (TTP), duration peak index (DPI), cure ascending slope (A), and area under the curve (AUC). The parameters combine with the dynamic process of nephrography and change of nephrography intensity to reflect blood flow characteristics and vessel features. Thus, contrast ultrasound was able to provide better tissue perfusion data [20]. Fischer has reported that 6 patients with acute renal rejection and 11 patients without rejection underwent an ultra sound (US) examination after intravenous bolus administration of an US contrast medium (SonoVue). It was found that a quantitative analysis of the arterial arrival of the US contrast agent in the early phase after renal transplantation was possible. This new US procedure might identify acute rejection earlier than traditional ultrasound techniques [21].

This study showed that the perfusion index of a transplanted kidney with normal renal function was better than that of a transplanted kidney with abnormal renal function. Furthermore, there was a significant difference between the slope rate of the cortical ascending curve (A1) and the medullary ascending curve (A2) and the derived peak intensity (DPI1) between the normal group and the abnormal group ($P < 0.05$). In addition, time-to peak (TTP1) was longer in the abnormal group, but there was no significant difference between the normal group and the abnormal group ($P > 0.05$). These results indicate that CEUS detected changes in microcirculation perfusion in the transplanted kidney with abnormal renal function. Moreover, blood perfusion data provided by CEUS correlated with renal function, which reflects the renal function of the transplanted kidney.

In conclusion, CEUS precisely manifested the renal parenchymal microcirculation feature. Moreover, ultrasound quantitative analysis is very useful in assessing tissue perfusion. Therefore, we consider CEUS as a new technique that monitors renal microcirculation exactly and conveniently and has many advantages, such as ideal imaging quality, being non-traumatic, and having no contraindications.

Disclosure of conflict of interest

None.

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References

[1] Du RR, Gao DP, Li Y and Chi H. The study of current situation of transplant kidney. J Med Res 2011; 40: 168-172.
[2] Ardelean A, Mandry D and Claudon M. Vascular complications following renal transplantation: diagnostic evaluation. J Radiol 2011; 92: 343-357.
[3] Heeger PS and Dinavahi R. Transplant immunology for non-immunologist. Mt Sinai J Med 2012; 3: 376-387.
[4] Sutherland T, Temple F, Chang S, Hennessy O and Lee WK. Sonographic evaluation of renal transplant complications. Med imaging Radiat Oncol 2010; 54: 211-218.
[5] Aktas S, Boyvat F, Sevmis S, Moray G, Karakayali H and Haberal M. Analysis of vascular complications after renal transplantation. Transplant Proc 2011; 43: 557-561.
[6] Dindyal S and Kyriakides C. Ultrasound microbubble contrast and current clinical applications. Recent Pat Cardiovasc Drug Discov 2011; 6: 27-41.
[7] McArthur C and Baxter GM. Current and Potential renal applications of contrast enhance ultrasound. Clin Radiol 2013; 67: 909-922.
[8] Kay DH, Mazonakis M, Geddes C and Baxter G. Ultrasonic microbubble contrast agents and the transplant kidney. Clin Radiol 2009; 64: 1081-1087.
[9] Piscaglia F, Nolsøe C, Dietrich CF, Cosgrove DO, Gilja OH, Bachmann Nielsen M, Albrecht T, Barozzi L, Bertolotto M, Catalano O, Claudon M, Clevert DA, Correas JM, D'Onofrio M, Drudi FM, Eyding J, Giovannini M, Hocke M, Ignee A, Jung EM, Klauser AS, Lassau N, Leen E, Mathis G, Saftoiu A, Seidel G, Sidhu PS, ter Haar G, Timmerman D and Weskott HP. The EFSUMB guidelines and recommendations on the clinical practice of contrast-enhanced ultrasound (CEUS): update 2011 on non-hepatic applications. Ultraschell in Med 2012; 33: 33-59.
[10] Harvey CJ, Sidhu PS and Bachmann Nielsen M. Contrast-enhance ultrasound in renal transplants: applications and future dircetions. Ultraschell Med 2013; 34: 319-321.
[11] Wang W, Li XB, Yin H, Yang XY, Liu H, Ren L, Hu XP, Wang Y and Zhang XD. Factors affecting the long-term renal allograft survival. Chin Med J (Engl) 2011; 124: 1181-1184.
[12] Irshad A, Ackerman S, Sosnouski D, Anis M, Chavin K and Baliga P. A review of sono-graphic evaluation of renal transplant complications. Curr Probl Diagn Radiol 2008; 37: 67-79.
[13] Burgos Revilla FJ, Marcen Letosa R, Pascual Santos J and López Fando L. The usefulness of ultrasonography and Doppler ultrasound in renal transplantation. Arch Esp Urol 2006; 59: 343-352.
[14] Brown ED, Chen MY, Wolfman NT, Ott DJ and Watson NE Jr. Complicatiomofrenal transplantation: evaluation with US and radionuclide imaging. Radiographics 2000; 20: 607-622.
[15] Radmehr A, Jandaghi AB, Hashemi Taheri AP and Shakiba M. Serial re-sistive index and pul-

satility index for diagnosing renal complications in the early posttransplant phase: improving diagnostic effi-cacy by considering maximum values. Exp Clin Transplant 2008; 6: 161-167.

[16] Tarzamni MK, Argani H, Nurifar M and Nezami N. Vascular complication and Doppler ultrasonographic finding after renal transplantation. Transplant Proc 2007; 39: 1098-1102.

[17] Nezami N, Tarzamni MK, Argani H and Nourifar M. Ultrasonographic indices after renal transplantation as renal function predictors. Transplantation 2008; 40: 94-96.

[18] Saracino A, Santarsia G, Latorraca A and Gaudiano V. Early assessment of renal resistance index after kidney transplant can help predict long-term renal function. Nephrol Dial Transplant 2006; 21: 2916-2920.

[19] Seiler S, Colbus SM, Lucisano G, Rogacev KS, Gerhart MK, Ziegler M, Fliser D and Heine GH. Ultrasound renal resistive index is not an organ-specific predictor of allograft outcome. J Nephrol Dial Transplant 2012; 27: 3315-3320.

[20] Oeltze S, Doleisch H, Hauser H, Muigg P and Preim B. Interactive visual analysis of perfusion data. IEEE Trans Vis Comput Graph 2007; 13: 1392-1399.

[21] Fischer T, Mühler M, Kröncke TJ, Lembcke A, Rudolph J, Diekmann F, Ebeling V, Thomas A, Greis C, Hamm B and Filimonow S. Early postoperative ultrasound of kidney transplants: evaluation of contrast medium dynamies using time-intensity curves. Rofo 2004; 176: 472-477.